Pharmacokinetics and haemodynamics of ketamine in intensive care patients with brain or spinal cord injury

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Background. Ketamine is used as an anaesthetic agent for short surgical procedures, and as a sedative and analgesic in intensive care patients. Intensive care patients with brain or spinal cord injury may have physiological changes that could alter the pharmacokinetics of ketamine. The pharmacokinetics of ketamine have been studied in healthy volunteers and in patients undergoing different types of surgery, but no data are available in intensive care patients.

Methods. We determined the pharmacokinetics of ketamine and its active metabolites, norketamine and dehydronorketamine, in 12 intensive care patients with brain or spinal cord injury. The effect of ketamine on haemodynamic variables was also investigated.

Results. The total clearance of ketamine, mean (SD), was 36.0 (13.3) ml min⁻¹ kg⁻¹, the volume of distribution (Vb) was 16.0 (8.6) litre kg⁻¹, and the elimination half-life was 4.9 (1.6) h. Ketamine did not alter any haemodynamic variables in the patients studied.

Conclusions. Pharmacokinetic variables of ketamine in intensive care patients are greater than in healthy volunteers and in surgical patients. The increase in the volume of distribution is greater than the increase in clearance, resulting in a longer estimated half-life of ketamine in this patient group.

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Ketamine is an anaesthetic agent characterized by a rapid onset and short duration of action. It is used for induction of anaesthesia in patients in the intensive care unit, for short surgical procedures, and for its sedative and analgesic properties.1,3 Blood pressure and spontaneous respiration are maintained under ketamine.1 Ketamine also has an important neuroprotective role and hinders the progression of cerebral ischaemia.4 In humans and in animals, ketamine is metabolized to two active metabolites, norketamine and dehydronorketamine.5,6 The pharmacokinetics of ketamine have been studied in healthy volunteers,7 8 and in patients undergoing general surgery.9 10 In intensive care patients, the majority of investigations on ketamine have evaluated its clinical effects, but no data are available on its pharmacokinetics. Hence, a study of the pharmacokinetics of ketamine and its metabolites is warranted in such patients.

Haemodynamic stability is essential in neurotraumatized or neurosurgical patients in the intensive care unit. A change in arterial blood pressure, especially hypotension, may aggravate neuronal damage in patients with brain trauma.11 Circulatory responses to ketamine have been studied in surgical patients.9 10 However, no data are available in intensive care patients. It has also been reported that ketamine increases intracranial pressure and cerebral blood flow in man.12 However, Schwedler and colleagues13 have shown that intracranial pressure and cerebral blood flow were unchanged during ketamine anaesthesia. In addition, when ketamine was administered, either in animals or in humans, during controlled ventilation, no increase in intracranial pressure was observed.14 15 Because of the potential benefits of ketamine in intensive care patients, and the lack of data about its effect on intracranial pressure, we have studied the pharmacokinetics of ketamine and its metabolites in these patients with brain or spinal cord trauma undergoing controlled ventilation. The effects of ketamine on systemic haemodynamics were also studied.
Methods

Patients

Twelve patients in the intensive care unit were included in the study. The procedure was approved by the university hospital ethics committee. Informed consent from each patient was obtained before enrolment into the study, except in one patient who was unconscious and consent was then obtained from his family. The patients presented with brain or spinal cord traumatic injury; two of them underwent neurosurgery before entering the intensive care unit. The administration of ketamine as an analgesic and sedative agent was required for painful interventions such as catheterization, tracheal intubation, and pleural drainage. The patients had a Glasgow coma score >12, except for the one patient who was unconscious and had a score of 10. Controlled ventilation was necessary for the patients because of pulmonary problems, pleural effusion or respiratory insufficiency. All patients had normal renal and hepatic function, except for one patient in renal failure with a creatinine clearance <20 ml min⁻¹. Four patients were chronic alcoholics (Table 1), and some were taking microsomal enzyme inhibitors during the study.

Table 1 Physical characteristics, clinical and pathological conditions of 12 intensive care patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Sex (M/F)</th>
<th>Pathology</th>
<th>Painful procedures</th>
<th>ASAT (IU litre⁻¹)</th>
<th>ALAT (IU litre⁻¹)</th>
<th>Bilirubin (μmol litre⁻¹)</th>
<th>Plasma protein (g litre⁻¹)</th>
<th>CL creatinine (ml min⁻¹)</th>
<th>Serum creatinine (μmol litre⁻¹)</th>
<th>Coexisting pathologies</th>
<th>Enzyme inhibitors</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>68</td>
<td>M</td>
<td>Spinal trauma, pneumothorax, thoracic vertebral fracture (T3 and T4)</td>
<td>Pleural drainage</td>
<td>25</td>
<td>81</td>
<td>14</td>
<td>17</td>
<td>390</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>28</td>
<td>69</td>
<td>M</td>
<td>Head trauma, haemothorax, pneumonia</td>
<td>Thoracic drainage</td>
<td>76</td>
<td>30</td>
<td>13</td>
<td>72</td>
<td>84</td>
<td>115</td>
<td>Chronic alcohol</td>
<td>Cimetidine 900 mg daily</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>80</td>
<td>F</td>
<td>Raised intracranial pressure</td>
<td>Head drainage</td>
<td>92</td>
<td>139</td>
<td>9</td>
<td>69</td>
<td>120</td>
<td>65</td>
<td>Chronic alcohol</td>
<td>Fluconazole 400 mg daily</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>70</td>
<td>M</td>
<td>Medullary trauma, paraplegia, paraplegia</td>
<td>Thoracic fracture</td>
<td>21</td>
<td>44</td>
<td>12</td>
<td>54</td>
<td>122</td>
<td>71</td>
<td>Anxiety</td>
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<tr>
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<td>64</td>
<td>80</td>
<td>M</td>
<td>Neurotrauma, pleural ablation</td>
<td>Pleural drainage</td>
<td>34</td>
<td>60</td>
<td>17</td>
<td>47</td>
<td>86</td>
<td>88</td>
<td></td>
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<tr>
<td>6</td>
<td>61</td>
<td>87</td>
<td>M</td>
<td>Head trauma, meningeal haemorrhage, pneumonia</td>
<td>Pleural drainage</td>
<td>29</td>
<td>38</td>
<td>12</td>
<td>65</td>
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<td>75</td>
<td>Chronic alcohol</td>
<td>Omeprazole 20 mg daily</td>
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<tr>
<td>7</td>
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<td>62</td>
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<td>Cervical trauma, tetraplegia</td>
<td>Tracheostomy</td>
<td>24</td>
<td>34</td>
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<td>91</td>
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<td>Chronic alcohol</td>
<td>Omeprazole 40 mg daily</td>
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<tr>
<td>8</td>
<td>29</td>
<td>55</td>
<td>F</td>
<td>Spinal trauma, acute respiratory insufficiency</td>
<td>Tracheostomy</td>
<td>15</td>
<td>62</td>
<td>10</td>
<td>52</td>
<td>135</td>
<td>48</td>
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<tr>
<td>9</td>
<td>25</td>
<td>67</td>
<td>M</td>
<td>Head trauma</td>
<td>Head drainage</td>
<td>58</td>
<td>115</td>
<td>84</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>86</td>
<td>M</td>
<td>Brain tumour, hydrocephaly</td>
<td>Head drainage</td>
<td>40</td>
<td>90</td>
<td>11</td>
<td>56</td>
<td>101</td>
<td>95</td>
<td>Ataxia</td>
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<td>11</td>
<td>21</td>
<td>70</td>
<td>M</td>
<td>Cerebral lesion</td>
<td>Head fracture</td>
<td>15</td>
<td>27</td>
<td>10</td>
<td>56</td>
<td>90</td>
<td>116</td>
<td></td>
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<tr>
<td>12</td>
<td>52</td>
<td>71</td>
<td>M</td>
<td>Neurotrauma</td>
<td>Tracheal intubation</td>
<td>22</td>
<td>84</td>
<td>16</td>
<td>55</td>
<td>96</td>
<td>81</td>
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</table>

ASAT=aspartate aminotransferase (normal range: 10–45 IU litre⁻¹); ALAT=alanine aminotransferase (normal range: 10–45 IU litre⁻¹).

Drug administration and collection of blood samples

Ketamine was administered as an i.v. bolus of 2 mg kg⁻¹ over 2 min, followed by an i.v. infusion of 2 mg kg⁻¹ h⁻¹ for 2 h. Samples of arterial blood were collected in heparinized tubes (5 ml), immediately before, during and after ketamine administration. These were obtained at the following time intervals: 5, 10, 15 and 30 min, and 1 h and 2 h after the bolus and during the infusion, and 1, 3, 5, 10, 15, 20, 30, 60 and 75 min, and 2, 3, 4, 5, 6, 8, 14, 20 and 24 h after the end of the infusion. After collection, blood samples were immediately centrifuged and the plasma was stored at −20°C until analysed.

Measurements of haemodynamics

Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and heart rate (HR) were continuously measured using an intra-arterial catheter (Seldicath® 4F–387613) purchased from Plastimed (Saint-Lieu-La-Forêt, France). The haemodynamic values were recorded each time the blood samples were obtained.
Chemicals
Ketamine, norketamine, dehydronorketamine and nortildine (internal standard) were supplied by Pfizer Laboratories (Paris, France). Solvents (Uvasol grade), and reagents were purchased from Elvetec (Lyon, France). Human serum Lyotrol® was purchased from Biomérieux (Lyon, France).

Drug assay
Ketamine, norketamine and dehydronorketamine were analysed according to the chromatographic method described by Bolze and Boulieu.16 The chromatographic system consisted of a Hewlett Packard 1050 series HPLC coupled with an HP Vectra 846/33M computer using HPChem software. The column used was a reversed-phase silica gel end-capped Purospher® RP-18e (5 μm) 125x4 mm purchased from Merck. Briefly, 1 ml of each sample was alkaline with boric acid (pH 13) and extracted twice with a mixture of dichloromethane:ethyl acetate (80:20, v/v) followed by back-extraction with 2 M HCl. After evaporation of the acid layer and reconstitution of the residue with the mobile phase, 60 μl was injected into the HPLC column. The quantification limit of the assay method was 5 ng ml⁻¹ for ketamine and norketamine, and 10 ng ml⁻¹ for dehydronorketamine. The intra-assay precision (%CV) was <5%, and the inter-assay precision (%CV) <7% for ketamine and its metabolites in the range of 10 to 5000 ng ml⁻¹.

Pharmacokinetic analysis
Pharmacokinetic analysis was done using PK-fit software.17 Compartmental analysis was used to obtain the following ketamine pharmacokinetic variables: volume of central compartment (V1), volume of distribution (Vβ), total clearance (CLt), area under the concentration–time curve (AUC), distribution half-life (T1/2a), and elimination half-life (T1/2b). Individual data were fitted independently and the quality of the fitted model was assessed by the presence of a random scatter of residuals, a minimal value for the Akaike and Schwartz criteria, and by the coefficient of variation of the estimated pharmacokinetic variables (CV% <20%). According to these criteria, a two compartmental model and a weighing factor of 1/Y²(predicted) was the most appropriate for all patients. For nortildine and dehydronorketamine, non-compartmental analysis was used to determine the maximum concentration (Cmax), time taken to reach Cmax (Tmax), AUC, and the half-life (T1/2). As no data are available about the fraction of ketamine metabolized into nortildine and dehydronorketamine in humans, the apparent clearance of these metabolites (CLm/fm) was calculated from the equation:

\[ \text{CLm/fm} = \frac{\text{CLt} \times \text{AUC}}{\text{AUCm}} \]

where fm is the fraction metabolized, CLt is the clearance of ketamine, and AUC and AUCm are the areas under the concentration–time curve of ketamine and its metabolites respectively, calculated from zero to infinity.

Statistical analysis
The statistical analysis was done using Graphpad Instat software. The repeated measures analysis of variance (ANOVA) test was used for multiple comparison of the haemodynamic variables at different time intervals. A paired t-test was used to compare the maximal change in the haemodynamic variables during ketamine administration with the baseline values. The non-parametric Spearman’s rank correlation test was used to study the correlation between pharmacokinetic variables (CLt, Vβ, T1/2) and pathophysiological variables (age, body weight, creatinine clearance, and bilirubinaemia).

Results
Pharmacokinetic results
Plasma ketamine concentration–time data were fitted satisfactorily to a two-compartment model (Fig. 1). The mean plasma concentration profiles of ketamine and its metabolites in 12 intensive care patients are shown in Figure 2. The mean T1/2a and T1/2b of ketamine were 0.27 h and 4.98 h respectively. The CLt mean (SD), as calculated by the ratio of the total dose to the AUC, was 36.0 (13.3) ml min⁻¹ kg⁻¹, V1 was 1.1 (0.6) litre kg⁻¹ and Vβ was 16.0 (8.6) litre kg⁻¹. For nortildine and dehydronorketamine, Cmax, Tmax, AUC and T1/2 were determined, and CLm/fm was calculated. Ketamine metabolites had longer half-lives than the parent compound (5.3 h for nortildine and 6.9 h for dehydronorketamine; Table 2). The Cmax of nortildine (1.0 mg litre⁻¹) and dehydronorketamine (0.59 mg litre⁻¹)
were observed at a $T_{\text{max}}$ of 1.6 h and 3 h respectively after ketamine administration (Fig. 2). The areas under the concentration–time curve (AUC$^{0-\text{inf}}$), for norketamine and dehydronorketamine were higher than for ketamine, indicating that the CLm is lower than that of the parent compound. CLm would reach a maximum value when the fraction metabolized is equal to unity. A large inter-individual variability in the pharmacokinetic profiles of these metabolites was observed. No statistically significant correlation ($P>0.05$) was observed between age, body weight, creatinine clearance, or bilirubinaemia and the ketamine pharmacokinetic variables. However, in patient one, ketamine clearance was low (11.4 ml min$^{-1}$ kg$^{-1}$). This patient was suffering from acute renal failure (creatinine clearance <20 ml min$^{-1}$). Patients two, three and six were chronic alcoholics who were taking microsomal enzyme inhibitors. The CLt of ketamine in these patients was 21.6, 42.2, and 47.6 ml min$^{-1}$ kg$^{-1}$ respectively. For patient seven, who was also a chronic alcoholic, but not taking microsomal enzyme inhibitors, the value of CLt of ketamine was 63.1 ml min$^{-1}$ kg$^{-1}$.

Transient side-effects were reported 5–15 min after the i.v. bolus injection of ketamine; one patient had stereotypic head movements, one patient had generalized fasciculations, and another had clonic muscle movements of the upper limbs.

**Haemodynamic results**

The haemodynamic responses after ketamine were studied in only nine patients. At the beginning of the study, the main objective was to study the pharmacokinetics, and then after the inclusion of the third patient, the study protocol was modified to investigate the effect of ketamine on haemodynamics. Mean (SD) baseline values of SAP, DAP and HR were 131 (25) mm Hg, 71 (16) mm Hg, and 76 (20) beats min$^{-1}$ respectively (Fig. 3). There was no statistically significant differences in SAP, DAP, and HR before and after ketamine administration over 26 h ($P>0.05$, ANOVA). Two group comparison of these variables at 10 min (maximum increase), and 960 min (maximum decrease) to baseline values showed no statistically significant difference ($P>0.05$, paired $t$-test), indicating that ketamine does not alter systemic haemodynamics in neurotraumatized intensive care patients.
Discussion

In 12 intensive care patients with brain or spinal cord injury, the pharmacokinetic profile of ketamine showed bi-compartmental behaviour. This is in accordance with that previously reported in healthy volunteers and surgical patients.78 18 The $T_{1/2a}$ was similar, but the $T_{1/2b}$ was longer than that reported in healthy volunteers (4.9 h vs 3 h) and that observed in patients undergoing minor surgery. The CLt of ketamine and the $V_b$ were high compared with values reported in healthy volunteers (CLt: 36.0 ml min$^{-1}$ kg$^{-1}$ vs 19.1 ml min$^{-1}$ kg$^{-1}$; $V_b$: 16.0 litre kg$^{-1}$ vs 5.1 litre kg$^{-1}$), and in surgical patients.78 10 18 The increase in $V_b$ was greater than the increase in CLt, resulting in a longer $T_{1/2b}$ of ketamine. No statistically significant correlation was observed between the pathophysiological (age, body weight, creatinine clearance or bilirubinaemia) and pharmacokinetic variables of ketamine in these patients. However, in patient one, ketamine clearance was low (11.4 ml min$^{-1}$ kg$^{-1}$), which might have been because of impaired renal function. In contrast, the high value of ketamine clearance in the alcoholic patients (patients three, six and seven) might be attributable to the inducing effect of alcohol on microsomal enzymes, in particular CYP3A4. It has been reported that CYP3A4 is the principal enzyme involved in ketamine metabolism.19 This enzyme can be induced by chronic alcohol intake.20 In patient two, the inducing effect of alcohol on CYP3A4 was not observed, possibly because the patient was taking cimetidine, a potent CYP3A4 inhibitor. But in patients three and six, ketamine clearance values were higher than those in non-alcoholics, despite therapy with omeprazole or fluconazole. It seems that the inducing effect of alcohol in these patients had more effect than the inhibitory effect of omeprazole or fluconazole on ketamine metabolism by microsomal enzymes. In fact, omeprazole and fluconazole are not potent inhibitors of CYP3A4.21 22 Thus induction of microsomal enzymes cannot fully explain the high values of ketamine clearance observed in the

Table 2 Pharmacokinetic variables, mean (SD) of ketamine, norketamine and dehydronorketamine in 12 intensive care patients with brain or spinal cord injury

<table>
<thead>
<tr>
<th>Ketamine</th>
<th>Structured model parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1$ (litre kg$^{-1}$)</td>
<td>$K_{21}$ (h$^{-1}$)</td>
</tr>
<tr>
<td>1.08 (0.57)</td>
<td>0.31 (0.17)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLt (ml min$^{-1}$ kg$^{-1}$)</td>
</tr>
<tr>
<td>36.0 (13.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolites</th>
<th>$T_{1/2}$ (h)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$C_{\text{max}}$ (mg litre$^{-1}$)</th>
<th>AUC$^{0-\text{inf}}$ (mg litre$^{-1}$ h)</th>
<th>CLm/fm (ml min$^{-1}$ kg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norketamine</td>
<td>5.32 (1.70)</td>
<td>1.61 (0.85)</td>
<td>1.00 (0.71)</td>
<td>6.29 (4.55)</td>
<td>19.2 (5.70)</td>
</tr>
<tr>
<td>Dehydroketroamine</td>
<td>6.91 (1.71)</td>
<td>2.98 (1.28)</td>
<td>0.59 (0.32)</td>
<td>4.97 (2.33)</td>
<td>24.3 (11.1)</td>
</tr>
</tbody>
</table>

Fig 3 Percentage change in haemodynamic variables during and after ketamine administration in nine intensive care patients with brain and spinal cord injury, as compared with values before drug administration (time 0). SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate. Data are mean ($\pm$SEM).
The half-lives of norketamine and dehydronorketamine were longer than that of ketamine. Norketamine was detected earlier, reached its peak level earlier and was eliminated faster than dehydronorketamine. Plasma concentrations and AUC of norketamine showed a large interindividual variability. This might be because of the interindividual variability in CYP3A4, the enzyme responsible for ketamine N-demethylation to norketamine.

Ketamine did not alter systemic haemodynamics in the patients studied. An alteration in haemodynamic variables has been observed with ketamine in surgical patients.9 In the present study, a temporary elevation in arterial concentrations and AUC of norketamine showed a large interindividual variability. This might be because of the CYP2B6 in cultures of human hepatocytes.

In conclusion, this preliminary study demonstrates that the pharmacokinetic variables of ketamine in intensive care patients with brain or spinal cord injury are relatively homogeneous. There is a need to conduct further clinical investigations on a larger number of similar patients to explain the pathophysiological factors causing the alterations in the pharmacokinetics of ketamine.

Acknowledgement
We thank Pfizer Laboratories (Paris, France) for providing us with ketamine, norketamine, dehydronorketamine and nortilidine.

References
5 Wootf TF, Adams JD. Biotransformation of ketamine, (Z)-6-hydroxyketamine and (E)-6-hydroxyketamine by rat, rabbit and human liver microsomal preparations. Xenobiotica 1987; 17: 839–47
15 Mayberg TS, Lam AM, Domino KB, Howard M, Win HR. Cerebral blood flow velocity and ADV02 response to ketamine in neurosurgical patients. Anesthesiology 1993; 79: A204